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Review

Seroepidemiology: an underused tool for designing and monitoring vaccination programmes in low- and middle-income countries

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Summary Seroepidemiology, the use of data on the prevalence of bio-markers of infection or vaccination, is a potentially powerful tool to understand the epidemiology of infection before vaccination and to monitor the effectiveness of vaccination programmes. Global and national burden of disease estimates for hepatitis B and rubella are based almost exclusively on serological data. Seroepidemiology has helped in the design of measles, poliomyelitis and rubella elimination programmes, by informing estimates of the required population immunity thresholds for elimination. It contributes to monitoring of these programmes by identifying population immunity gaps and evaluating the effectiveness of vaccination campaigns. Seroepidemiological data have also helped to identify contributing factors to resurgences of diphtheria, *Haemophilus Influenzae* type B and pertussis. When there is no confounding by antibodies induced by natural infection (as is the case for tetanus and hepatitis B vaccines), seroprevalence data provide a composite picture of vaccination coverage and effectiveness, although they cannot reliably indicate the number of doses of vaccine received. Despite these potential uses, technological, time and cost constraints have limited the widespread application of this tool in low-income countries. The use of venous blood samples makes it difficult to obtain high participation rates in surveys, but the performance of assays based on less invasive samples such as dried blood spots or oral fluid has varied greatly. Waning antibody levels after vaccination may mean that seroprevalence underestimates immunity. This, together with variation in assay sensitivity and specificity and the common need to take account of antibody induced by natural infection, means that relatively sophisticated statistical analysis of data is required. Nonetheless, advances in assays on minimally invasive samples may enhance the feasibility of including serology in large survey programmes in low-income countries. In this paper, we review the potential uses of seroepidemiology to improve vaccination policymaking and programme monitoring and discuss what is needed to broaden the use of this tool in low- and middle-income countries.

keywords seroepidemiology, seroprevalence, vaccines, vaccine-preventable diseases, developing countries, surveillance

Introduction

Seroepidemiology, the collection and use of data on the prevalence of antibodies (or less frequently, antigens) in serum or related fluids to study the distribution and determinants of infection, is a potentially powerful tool to help design and monitor vaccination programmes [1, 2]. Its application to individual vaccine-preventable diseases (VPDs) depends on whether there is a serological marker of past infection or vaccination, whether vaccine-induced antibody can be distinguished from that following infection, the extent and duration of protection conferred by antibody, and whether the antibody level that correlates with protection is known [3]. To date, seroepidemiology has contributed most to the control and elimination of poliomyelitis, measles and rubella – acute viral VPDs where long-lasting immunity follows infection or their respective replicating vaccines – but it has also contributed to adapting vaccination strategies for non-replicating vaccines, including diphtheria, *Haemophilus influenzae* type B (Hib) and pertussis in high-income countries.

Challenges around specimen collection from representative populations, standardised high-quality conduct of laboratory assays and appropriate statistical analysis have limited the use of seroepidemiology in low- and middle-income countries. The need for accurate data on population immunity is increasing, however, as programmes move towards eradication of poliomyelitis and elimination of measles and rubella, and also need to adapt to maintain long-term control of other VPDs.

In this paper, we provide an overview of the use of seroepidemiology to design, monitor and adapt strategies for VPDs, briefly review the requirements to obtain high-quality data and draw appropriate programmatic conclusions and discuss how to increase its use in low- and middle-income countries. The use of serological endpoints in clinical trials of different vaccines, schedules or routes of administration, another important application of serology to vaccine programme design, is beyond the scope of this paper.

Uses of seroepidemiological data for vaccination programme design and monitoring

Uses of seroepidemiology before vaccination is introduced

For acute, antigenically stable infections, data on antibody prevalence by age are used in mathematical models to estimate the age-specific force of infection, the burden of disease (BOD) and theoretical immunity thresholds for elimination of infection.

Seroprevalence data (Table 1) have been most important for infections such as hepatitis B and rubella that are frequently subclinical yet have a measurable serological marker of infection. In the case of hepatitis B virus (HBV), the viral surface antigen (HBsAg) is measured whereas for other infections, specific antibody is used. The outcomes of HBV infection are age-dependant and include asymptomatic infection, acute hepatitis B illness or chronic HBV infection, which predisposes to cirrhosis and hepatocellular carcinoma [4]. Because data from developing countries on chronic liver disease and cancer are scarce, seroepidemiological data were critical to estimate global disease burden and vaccination impact. WHO classified countries into high (≥8%); medium (2–7%) or low (<2%) levels of endemicity according to the prevalence of HBsAg, an indicator of chronic HBV infection. In 1992, WHO recommended that HBV vaccine be introduced in highly endemic countries by 1995 and in all countries by 1997 [5]. Using data on the seroprevalence of hepatitis B in a large number of countries, mathematical modelling predicted that approximately 1.4 million HBV-related deaths would occur in the 2000 global birth cohort in the absence of vaccination, and 90% of these could be avoided through routine HBV vaccination starting at birth with 90% coverage [6].

Hepatitis A infection causes substantial morbidity in high-income countries and is increasingly recognised as important in middle and low-income countries. Infection commonly manifests with acute hepatitis in adults but is frequently subclinical in children under age 5 years. Seroepidemiological studies of antibody prevalence have been used to describe the epidemiology of hepatitis A virus and identify countries (e.g. middle-income) or groups (e.g. travellers) where vaccination may be most relevant [7, 8].

Rubella infection in children and adults is frequently subclinical or mild and until recently was not notified in low-income countries. Estimates of the global burden of congenital rubella syndrome and the potential impact of vaccination strategies are therefore based on models of the age-specific force of infection derived from studies of the prevalence of rubella antibody, which persists lifelong after infection. From seroepidemiological data reviewed up to 1997, the global BOD was estimated at approximately 110 000 cases (plausible range 14 248–308 438 cases) of CRS per year [9], and little changed by 2010, when 105 000 (95% CI: 54 000–158 000) CRS cases were estimated globally [10].

Seroepidemiology also provides additional information to complement clinical surveillance for VPDs for which the sensitivity of reporting may be low and vary by age group, geography or other factors affecting access to care. Thus, serosurveys have helped describe the pre-vaccination epidemiology of varicella [11–15], yellow fever [16] and seasonal [17, 18] or pandemic [19] influenza. Serological data are less useful for VPDs that do not always generate robust serum antibody responses (e.g. cholera, human papillomavirus, rotavirus, typhoid) or for invasive bacterial infections [*Haemophilus influenzae* type b (Hib), meningococcal and pneumococcal infection] where antibodies generated by colonisation complicate the interpretation of seroprevalence data [3]. Nonetheless, serological studies have contributed to elucidating the pre-vaccination epidemiology of meningococcal A infection in Africa [20].

Uses of seroepidemiology after vaccination is introduced

Vaccination programme managers and their partners typically set targets for control or elimination of VPDs and monitor progress via disease surveillance and vaccination coverage measurement. These two sources of data are combined to estimate the proportion of each birth cohort that is protected, but the resulting estimates may be biased by inaccurate coverage measurement [21], low

Table 1 Uses of seroepidemiology to guide the control and elimination of vaccine-preventable diseases (VPDs)

Potential use of seroepidemiological data	Requirements	Examples of vaccine-preventable diseases where used	Comments
Pre-vaccination			
Estimate burden of disease	Either antigen or antibody correlates with infection. Known natural history of infection	Hepatitis B Rubella Contributed to hepatitis A, measles, varicella, yellow fever	Most useful for diseases which are subclinical, underrecognised or undernotified, but also contributes to better analysis and interpretation of clinical surveillance data
Estimate theoretical herd immunity thresholds	Age profiles of seroprevalence indicate age profile of acquisition of infection (i.e. protective antibody follows infection and is stable over time)	Hepatitis B, measles, rubella, poliomyelitis	Disease surveillance is an alternative source of data on age-specific infection rates but seroprevalence data are especially helpful for infections that are often subclinical
After vaccination is introduced			
Identify which age groups to include in campaigns	Age profiles of seroprevalence indicate which age groups lack immunity, taking into account waning antibody levels after vaccination in the absence of natural boosting	Measles, rubella, poliomyelitis	Seroprevalence data could be used more often to show which age groups need campaigns to eliminate infection transmission
Determine the duration of immunity after the primary series, the need for and timing of booster doses	Antibody is main correlate of protection	Diphtheria, Hib, Meningococcus, Pertussis, Tetanus	Long-term prospective follow-up of vaccine trials rarely feasible hence seroprevalence studies (often triggered by disease resurgence) contribute to decisions on including booster doses to children and/or adults in national schedules
Monitor progress towards elimination and identify population gaps in immunity	Targets have been set for required prevalence of antigen or antibody Antibody is main correlate of protection	Hepatitis B, measles, rubella, poliomyelitis, tetanus	Clinical and epidemiological relevance of waning antibody levels after vaccination need to be understood, otherwise population immunity may be underestimated by seroprevalence data

Table 1 (*Continued*)

Potential use of seroepidemiological data	Requirements	Examples of vaccine-preventable diseases where used	Comments
Investigate causes of resurgence of disease	Antibody is main correlate of protection	Diphtheria, Hib, Meningococcus, Pertussis	Disease surveillance may detect apparent increases in incidence or outbreaks. Serological data helpful to investigate potential causes, for example changes in diagnostic or reporting patterns, waning immunity or reduced vaccine effectiveness following changes in vaccine formulations or schedules
Evaluate impact of campaigns	Can account by study design (e.g. pre- and post-campaign surveys) and/or analysis for antibody due to natural infection or routine immunisation	Measles, rubella, poliomyelitis	Can be used for other vaccines administered by campaigns. Without pre-campaign serology, may be hard to know the effect of the campaign itself but can determine whether target immunity prevalence has been reached
Estimate vaccine coverage	There is an antibody correlate of vaccination No natural infection OR can distinguish antibody induced by vaccine from that by infection or colonisation Predictable immunogenicity under wide range of programme conditions Antibody of known duration (study appropriate age group) Antibody levels correlate with number of doses received	Potential candidates are as follows: Tetanus toxoid Hepatitis B vaccine Measles, rubella, poliomyelitis in settings where infection has been eliminated	Apart from hepatitis B and tetanus, often difficult to exclude natural infection. The presence of antibody does not tell you how many doses have been received even when natural infection can be excluded. The absence of antibody does not mean that the child was not vaccinated as no vaccine is 100% effective even in ideal conditions. Poor vaccination practices can reduce effectiveness, and antibody levels wane over time. Therefore difficult to use seroprevalence data to evaluate accuracy of reported coverage data

vaccine effectiveness or duration of protection, or changes in the sensitivity and specificity of surveillance over time. Seroprevalence studies allow direct measurement of the age-specific profile of susceptibility if the assays are of known, and adequate, sensitivity and specificity and representative population samples are studied. Data on age-specific seroprevalence are important to monitor overall programme progress, identify population groups where immunity is low and inform targeted vaccination strategies such as campaigns and/or

inclusion of booster doses in national schedules. They can help to elucidate reasons for outbreaks and evaluate the impact of vaccination campaigns on population immunity. There is also great interest in using serological data to infer routine vaccination coverage [22].

Hepatitis B control

WHO recommends that all regions and associated countries develop goals for hepatitis B control appropriate to their epidemiological situation [23]. The Western Pacific Region and Eastern Mediterranean Region have established goals of reducing HBsAg prevalence to <1%. Serosurveys of HBsAg prevalence are the primary tool to measure vaccination impact [23, 24]. Serosurveys have also confirmed long-term protection against chronic infection (e.g. 94% vaccine effectiveness at approximately 20 years after vaccination in The Gambia [25]), despite frequent occurrence of hepatitis infection among fully vaccinated individuals. Such infection does not lead to carriage or complications and the WHO therefore does not recommend booster doses of HBV [23].

Measles and rubella elimination

The European region has established age-specific immunity targets for measles taking account of different contact patterns between different age groups [26]. Many European countries collect serological data on multiple infections periodically through the European Seroepidemiology Network (ESEN), as do Australia and the United States. Some countries collect sera via periodic community-based surveys while others have systems to store the residues remaining from microbiological or biochemical investigations at participating laboratories and sample these. Seroepidemiological data for 17 European countries between 1996 and 2004 identified which were on track to achieve measles elimination and which were at risk of localised outbreaks or large epidemics [26]. Unfortunately, these data were not acted on in time to avoid outbreaks in most of the countries identified at risk [27, 28]. In Australia, data from three national serosurveys between 1996 and 2007 showed that measles population immunity targets had been reached and sustained, supporting evidence from coverage estimates, disease notifications and genotyping showing that measles has been eliminated [29]. In developing countries, seroepidemiological surveys in the 1990s identified age groups and other risk groups with low prevalence of immunity [30–32] and more recently have been used in Cambodia to show that target levels of immunity for elimination have been reached [33].

For rubella, ESEN data from 1994 to 1998 [34] and from 1996 to 2004 [35] showed that despite the low reported incidence in many countries, population immunity was inadequate for elimination. Countries were advised to conduct catch-up campaigns in older age groups and selective targeting of older females to ensure the necessary levels of protective immunity among women of childbearing age. In Australia, national serosurveys provided estimates of the effective reproductive rate for rubella of <0.5, well below the epidemic threshold of 1, supporting the evidence from disease surveillance of elimination [36]. In Singapore, selective vaccination of schoolgirls began in 1976 and infant measles–rubella vaccination in 1990, with additional catch-up vaccination programmes [37]. Successful programme implementation has been shown by consistently high rubella vaccine coverage, a marked fall in reported cases of acquired rubella to below the regional target of <10 per million population, and the absence of indigenous CRS cases in 2012 and 2013 [37]. These data are supported by regular seroepidemiological surveys that confirm a fall in susceptibility among women of childbearing age, from 44% in 1975 to 28% in 1985 [38] to 11% in 2013 [37]. Rubella incidence and susceptibility of adult women were, however, both higher in migrants than in Singapore citizens, and further efforts to protect adult women are urged.

Poliomyelitis eradication

As for measles and rubella, seroepidemiology is used to determine if poliomyelitis immunity targets have been reached, either at national-level or in high-risk areas of endemic or recently endemic countries [39–41], allowing better targeting of campaigns. Serosurveys have been used to evaluate the use of bivalent oral polio vaccine (OPV) in campaigns [42] and to predict the cost-effectiveness of expanding the age range of campaigns [43].

In countries or regions that have eliminated wild poliovirus transmission, seroepidemiology is useful to predict the risk of transmission after importations [44–46]. Studies have helped to assess factors contributing to polio outbreaks. In the Democratic Republic of Congo, residual sera were available from HIV sentinel site surveillance of pregnant women collected before an atypical outbreak of wild poliovirus type 1 (WPV1) affected young adults in 2010–11. Sera were assayed for antibodies to polioviruses, and results showed that there had been immunity gaps in women aged 15–29 years in the two provinces with the highest numbers of cases in adults [47]. In Cambodia, a large national population-based serosurvey identified immunity gaps in young women, highlighting the

need for continued vigilance and surveillance [33]. In Tajikistan, a large outbreak of WPV1 followed importation in 2010, leading to outbreak response vaccination with monovalent OPV type 1 vaccine (mOPV1) followed by trivalent OPV (tOPV) campaigns. A nationwide serosurvey of 1–24-year-olds performed after the mOPV1 campaign but before the tOPV campaign showed high prevalence of antibodies to type 1 poliovirus in all ages, suggesting that the outbreak response had been effective, but low prevalence of antibodies to type 3 poliovirus, particularly in birth cohorts that had not been targeted in previous campaigns and in certain regions. This suggested that the outbreak resulted from suboptimal vaccine coverage over a long time period, particularly in areas vaccinated only via routine services [48].

A major event in the polio eradication programme in 2016 is the global switch from trivalent to bivalent OPV and at least one dose of inactivated polio vaccine (IPV). Seroepidemiology is crucial to provide baseline data on population immunity and to monitor any changes after the switch [49–51].

Other vaccine-preventable diseases

Serosurveillance of meningococcal serogroup C antibodies in the United Kingdom (UK) has shown that antibody levels wane quickly after primary vaccination [52], highlighted the relationship between waning antibody titres and declining vaccine efficacy [53] and shown the need for a booster dose to be administered [54]. Seroepidemiology is likewise being used to help monitor the impact and duration of immunity after introduction of the new conjugate meningococcal A vaccine in Africa [20, 55]. Diphtheria, once a major cause of childhood mortality in Europe, became uncommon after mass vaccination began and was targeted for elimination from the region by 2000, but a major resurgence occurred in all countries of the former Soviet Union during the 1990s [56]. Serosurveillance for diphtheria coordinated through ESEN from 1996 showed that many other European countries had high proportions of adults with antibody levels below the putative protection threshold; some childhood vaccination schedules and vaccine formulations were less immunogenic than others; booster doses of tetanus diphtheria (Td) vaccine were important to maintain immunity; and continued vigilance was indicated to ensure high coverage and effectiveness of childhood vaccination [57, 58]. Similar lessons have recently been reported from serosurveys performed after outbreaks occurred in Thailand and Indonesia [59, 60]. In Tajikistan, where incidence had been low since mass campaigns had controlled the resurgence of the 1990s, a survey in 2010 showed that only about one-third of 10–19-year-olds were immune to diphtheria, leading to a national Td campaign of 3–21-year-olds in 2012 [61].

Seroepidemiology has helped to identify contributing factors to resurgences of Hib in the UK and pertussis in several industrialised countries. In the UK, serological data helped to demonstrate that protection after primary Hib vaccination in infancy did not last as long as expected, especially after use of a less immunogenic acellular pertussis-containing combination Hib conjugate vaccine (DTaP-Hib) during 2000–2001. This led to catch-up vaccination programs and a change in booster dose policy [62]. In the case of pertussis, high antipertussis toxin (PT) titres (>125 units/ml or >65.5 units/ml) are taken as evidence of infection within the last year, because vaccines rarely lead to such sustained high antibody levels [63], although it may be difficult to use the data to estimate disease incidence in young infants soon after vaccination [64]. Diagnostic methods for pertussis vary within and between countries and may vary by age group. Seroprevalence data are used to estimate true disease incidence (often giving incidence rates several 100-fold higher than those reported via clinical surveillance), to conduct cross-country comparisons [64] and to identify age groups contributing to disease transmission [65]. Serosurveillance of pertussis in seven European countries showed that pertussis incidence was related to low vaccine coverage in some populations and to waning immunity in high-coverage countries [66]. When combined with either data from surveys on social mixing patterns or with data from previous longitudinal studies on the decay rate of antibody after infection, seroepidemiological data have been a powerful tool to estimate the force of infection and the basic reproductive number of pertussis. Data on pertussis toxin titres from cross-sectional surveys conducted before the introduction of adolescent booster doses in five European countries led to estimated infection incidence between 1% and 6% per year with peaks in adolescents and to a lesser extent in young adults. This suggested ongoing subclinical circulation of pertussis due to waning of immunity after both vaccination and infection [67].

Evaluation of vaccination campaigns

Serosurveys conducted after campaigns are helpful to show whether immunity targets have been reached and assess whether the appropriate age groups were targeted by the campaign by measuring susceptibility in other age groups. For example, serosurveys in Niteroi, Brazil, in 1996 and in England and Wales in 1994 showed that catch-up campaigns successfully reduced susceptibility to

measles to very low levels in the target age groups [68, 69]. In Australia, a campaign targeting school-age children also achieved low susceptibility targets [70] but a less-well funded or advertised programme targeting adults aged 18–30 years failed to reduce susceptibility in Victoria State and subsequent outbreaks continued to affect young adults [71]. A serosurvey conducted 3 years after a measles vaccine campaign in Lusaka, Zambia, showed the rapid build-up of susceptible children after the campaign and confirmed lower vaccine effectiveness in HIV-infected than HIV-uninfected children (Moss 2009). Serosurveys have also been used to evaluate the impact of campaigns on population rubella immunity [72, 73].

To evaluate campaigns, pre- and post-campaign surveys are ideal but to date have only been feasible on a small scale. Studies using oral fluid assays in Ethiopia [74] and Kenya [75] showed that measles campaigns reduced susceptibility by 75% and 70%, respectively, although target immunity levels were not reached in Ethiopia, and older children who had not been included in the campaign had high susceptibility.

Estimation of routine vaccination coverage

Vaccination coverage measurement is a critical part of monitoring programme performance but both routine reports and community-based surveys are subject to many potential biases [21, 76, 77]. There is therefore interest in using seroprevalence as an indicator of coverage of infant or adult vaccination. To infer vaccination coverage from seroprevalence data, either there must be no natural infection occurring in the area or antibody induced by vaccine should be distinguishable from that following infection; there should be known vaccine immunogenicity under a wide range of programme conditions, antibody should have known duration after primary vaccination and the appropriate age group should be studied, and antibody levels should correlate with the number of doses of vaccine received and be identified precisely and accurately by a field-friendly assay [21, 22].

Vaccine-induced immunity can only be distinguished from natural immunity for tetanus, hepatitis B and in certain settings for poliomyelitis, measles and rubella where natural infection has been eliminated. Serosurveys have a potentially important role in monitoring progress towards elimination of neonatal tetanus, because it is especially difficult to use vaccination coverage data to predict the proportion of women of childbearing age or the proportion of live births that are protected against tetanus. Tetanus toxoid-containing vaccines are recommended throughout life, the primary series being given in infancy and booster doses thereafter, with a cumulative total of 5 or 6 doses (depending on the schedule) considered to offer protection through at least the childbearing years. Irrespective of childhood vaccinations, in developing countries, pregnant women are usually offered two doses of tetanus toxoid vaccine during each pregnancy but cards are rarely kept, and information on doses received prior to the current pregnancy derives from maternal reports in community-based surveys. A serosurvey in the Central African Republic showed that the proportion of neonates protected at birth was substantially underestimated using reported data on vaccinations received compared to tetanus antibody prevalence in mothers [78]. Data on the prevalence of tetanus antibody are therefore a better indicator of population immunity and the likelihood that neonatal tetanus has been eliminated [79].

It is difficult, however, to use seroprevalence data in any age group to estimate vaccine coverage because the absence of detectable antibody may indicate not having been vaccinated or alternatively an insensitive assay, low vaccine effectiveness or waning antibody levels after vaccination. The presence of antibody does not indicate how many doses of vaccine were received, or whether they were received in routine services or campaigns. For example, in a recent study in three districts of Ethiopia, postulated protective levels of tetanus antibodies were found in 67–94% of infants who had two documented doses of pentavalent vaccine and in 80–95% of infants with three documented doses, and even in those with only one documented dose, 40–80% had 'protective' levels [80]. Attempts to correlate tetanus antibody prevalence with coverage of different vaccines will be further complicated in countries that have conducted campaigns using group A conjugate meningococcal vaccine having a tetanus toxoid carrier because this vaccine also stimulates tetanus immunity [81, 82].

Although of limited use to measure vaccine coverage, measles serosurveys can highlight potential problems with storing, administering or recording measles vaccination. A recent study in poor areas of Mexico and Nicaragua found that high proportions of children aged 12–23 months with documented measles vaccination were seronegative and that these children were clustered in certain municipalities, raising concerns about vaccination practices in those areas [83].

Discussion

Seroepidemiology can be a powerful tool to guide decision-making on vaccine introduction and vaccine schedules and to monitor programme impact, particularly when combined with mathematical modelling. If assays

are sufficiently sensitive and specific, then population immunity is measured directly, rather than being inferred from imperfect measures of vaccination coverage and insensitive disease surveillance. Repeated serosurveys can better assess geographical and temporal trends than disease notification, which is dependent on health worker practices and diagnostic test performance [65, 84, 85]. In settings where infections are eliminated or near elimination and there are very few disease notifications, serosurveillance can detect immunity gaps before outbreaks occur. Causes of immunity gaps include failure to vaccinate certain population groups [33, 86–90], in-migration of unvaccinated persons [90, 91], reduced vaccine effectiveness [83, 92] or waning vaccine-induced immunity [93, 94]. Ideally, immunity gaps are identified in time to prevent outbreaks. Coordinated and standardised serosurveillance across Europe and in Australia has allowed comparison of the effectiveness and impact of different vaccine formulations and schedules for diphtheria, Hib and pertussis, and guided supplementary immunisation activities against measles, polio and rubella.

Seroepidemiology has much potential for low-income countries, to estimate hepatitis B and rubella burden and monitor vaccination impact, identify age groups for vaccination campaigns against measles, polio and rubella, investigate the need for and timing of booster doses of diphtheria, Hib, pertussis and meningococcal vaccines, monitor protection against tetanus in adult women and their babies and identify populations at risk of outbreaks of VPDs. Serosurveys are of increasing importance in the end game of polio eradication, to identify high-risk areas within large countries, to monitor the effectiveness of targeted campaigns and to monitor population immunity after changes in vaccine formulations and schedules. Although seroprevalence of a given antibody cannot currently, for reasons outlined earlier, validate other measures of vaccination coverage, it can give a direct measure of programme effectiveness in reaching target population immunity levels.

Despite these potential applications, the use of seroepidemiology in low-income countries is limited by access to high-quality laboratories and appropriate assays, and logistical, communication, time and resource challenges in conducting surveys that are representative of the populations of interest and have adequate participation rates, especially if venous blood samples are required [22, 95]. Experience with less invasive specimens such as dried blood spots (DBS) or oral fluid has been mixed. Oral fluid performed well in studies in Ethiopia [74, 96] and Kenya [75] but poorly in Bangladesh [97]. A study using DBS in poor areas of Mexico and Nicaragua found very low measles antibody prevalence (68% and 50%, respectively) despite high reported vaccination coverage and successful measles elimination in both countries [83]. Although the study showed internal consistency in that antibody prevalence was lowest in areas with known cold chain or vaccination recording problems, it is hard to reconcile this low prevalence with the absence of measles outbreaks. Suboptimal assay sensitivity cannot be ruled out under the field conditions of DBS collection, which differed from those in the prior validation study of DBS compared to serum. In the Democratic Republic of Congo, the prevalence of both measles and tetanus antibodies measured on DBS samples during the 2013–2014 Demographic and Health Survey was also far below that expected (http://dhsprogram.com/pubs/pdf/FR300/FR300.vpd.pdf, 21 February 2016). National measles seroprevalence in children aged 6–59 months was 64.4%, and although seroprevalence did rise with age as expected in this country with ongoing large measles outbreaks [98], the finding of only 50% seropositivity in some of the provinces worst affected by the outbreak raises questions about assay sensitivity. Similarly, the prevalence of tetanus antibodies was very low and did not increase according to numbers of doses of vaccine received, even among children whose vaccination card was seen. Neither of these large surveys included a subsample for assay by gold standard assays on serum from venous blood samples, which would allow validation of the assay performance under the field conditions of the survey.

The situation is evolving, however, as laboratory and field epidemiology capacity has expanded through global laboratory networks for polio, measles [99], rubella and others and epidemiology training programs [100, 101]. Well-conducted population-based surveys can achieve high participation rates and although costly, usually provide data on multiple infections. Large-scale community-based surveys are performed regularly in most developing countries [102] and have shown the feasibility of collecting capillary blood samples [103]. Developments in multiplex assays [79] will allow simultaneous assessment of immunity to several antigens of interest in surveys. It will nonetheless be good practice to include collection of venous blood samples on a subsample for gold standard assays with appropriate use of international reference standards.

Improvement of assays that use minimally invasive specimens such as oral fluid or DBS could increase the acceptability of repeat surveys, which are preferable for assessing vaccine coverage [104], vaccine immunogenicity and campaign impact. In countries with high attendance at health services, sentinel site surveillance may be adequate to monitor trends, for example, in

rubella and tetanus susceptibility among adult women [105], as is performed for monitoring trends in HIV [106].

Estimates of the spatiotemporal dynamics of individual and population immunity to a variety of pathogens would be a powerful tool for public health programmes and will be facilitated by further improvements in laboratory assays to make them more user-friendly in low-income settings [79], standardising laboratory assays to make it easier to compare studies in different locations [107], continuing development of statistical approaches to analysing serological data including accounting for waning antibody levels over time [108, 109], and studies to clarify the relationship between antibody levels, the number of doses of multidose vaccines received and the duration since the last dose.

When considering undertaking a seroepidemiological study, it is important to choose the priority public health questions to which serology can contribute most and hence the antigens/antibodies to be studied, identify the populations of interest and the sampling method most likely to provide a representative sample of those populations, select the most appropriate laboratory assays to use – balancing field friendliness with performance characteristics and planning to use gold standard assays at least on a subsample – and determine how data will be managed, analysed and used. Although seroepidemiology is regarded as an essential part of comprehensive immunisation programme monitoring in many industrialised countries, they are experiencing financial and technical challenges to sustaining high-quality serosurveillance systems [2, 110]. Further experience is needed to determine the feasibility, acceptability, cost and most useful applications of seroepidemiology in low-income countries.

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